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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,215	03/31/2006	Simon Goodman	MERCK-3151	9265

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
09/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/574,215	GOODMAN ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5 pages / 03/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on July 6, 2009.

Election/Restrictions

Applicant's election of 3-{3benzyloxy-2-[5-(pyridine-2-ylamino)-pentanoylamino]-propanoylamino}-3-(3,5-dichloro-phenyl)-propionic acid (EMD 409849) as the alpha vbeta6-integrin antagonist and secondary biliary liver fibrosis as the specific pathological condition in the reply filed on July 6, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a).

Status of Claims

Cancellation of claims 1-9 and addition of claim 10 is acknowledged.

Claim 10 is currently pending and is the subject of this office action.

Claim 10 is presently under examination.

Priority

The present application is a 371 of PCT/EP04/10396 filed on 09/16/2004, and claims priority to foreign application: EPO 03022048 filed on 10/01/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention

Claim 10 recites a method for treatment of secondary biliary liver fibrosis by administering to a patient a therapeutically effective amount of the alphavbeta6-integrin antagonist EMD 409849.

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The state and predictability of the art

As illustrative of the state of the art regarding the treatment of liver fibrosis with alphavbeta6-integrin antagonists, the examiner cites: Murphy et. al. (Expert Opinion on Investigational Drugs (2002) 11:1575-1585) and Nejjari et. al. (Journal of Pathology (2001) 195:473-481).

Murphy teaches that liver fibrosis represents a major worldwide healthcare burden (see abstract). Current therapy is limited to removing the casual agent (see page 1576, topic 2). This is most effective when instituted in the early stages of hepatic fibrosis with the potential resolution of the liver to near normal histology. This approach is effective in chronic hepatitis B and C virus infection, iron overload, copper overload, autoimmune chronic active hepatitis, schistosomatosis and secondary biliary fibrosis (see page 1576 under topic 2.). Hepatic Stellate Cells (HSC) have been recognized to be responsible for the synthesis of much of the excess extracellular matrix observed in chronic liver diseases and as such have merged as a new therapeutic target for the treatment of liver fibrosis (see page 1576, under topic 3.). Among the therapeutic agents the authors mention: agents directed to reduce hepatic injury like colchicine (see 3.1 on page 1576), inhibitors of hepatic stellate cell activation and proliferation (see 3.2),

antioxidants (see 3.3) etc. However there is no mention of any type of integrins. In section 6, on page 1580 the authors give a profile of the ideal antifibrotic drug:

1- It should effectively reduce excess collagen within the liver without affecting extracellular matrix turnover elsewhere in the body,

2- It should be liver specific: it will need to have a useful and safe drug carrier,

3- It should have minimal side effects on existing hepatic function, cardiovascular system and blood coagulation system,

4- It should be tolerated by the immune system rather than influencing its activity,

5- It should be a single therapy working at multiple mechanistic levels,

Etc.

The authors finally conclude; "the detailed understanding of the cell biology of the activated HSC has paved the way to the rational design of novel antifibrotic therapies. A number of strategies have been shown to be effective in vitro and animal models. These include: antioxidants, cytokine modulators, antiproliferative drugs, etc. The ideal antifibrotic agent is yet to come; nevertheless, such an agent will inevitably be developed given the multiple therapeutic targets that are known with stellate cell biology (see section 7 on page 1581).

Regarding the association of integrins with chronic liver diseases, Nejjari teaches that integrins are membrane receptors mediating the structural and functional interactions of epithelial and mesenchymal cells with the extracellular matrix. Integrins are heterodimeric membrane proteins composed of two chains, denoted alpha and beta. At least 18 different alpha and eight different beta chains are currently known.

Their various combinations result in more than 20 functional integrin dimmers differing in their distribution and ligand specificity. The integrin repertoire expressed by hepatocytes is highly distinctive. In contrast to most epithelial cells, normal adult human hepatocytes express low levels of only three integrin dimmers: alpha1beta1, alpha5beta1, and alpha9beta1. In chronic liver disease, the integrin repertoire of liver cells is markedly altered. Alterations include the up-regulation of some of the integrin receptor expressed in the normal state, and de novo induction of normally undetectable integrin receptors such as alpha6beta1 (see introduction). There is no mention that alphavbeta6-integrin is over expressed in chronic liver disease.

From these references it can be concluded that the art of treating liver fibrosis in general and in particular with alphavbeta6-integrin antagonists is very unpredictable.

4. The amount of direction or guidance provided and the presence or absence of working examples

The specification shows examples of the effect of the alphavbeta3-integrin antagonist EMD 409915 on cell migration on: a) CFSC-2G cells, a rat HSC cell line, b) primary rat HSC/MF treated with PDGF-BB (see Fig. 1 and page 7) and c) on fetal calf serum (FCS) (see Figure 2 and page 7 of the specification); and the expression of a) beta3integrin and b) beta6 integrin in liver fibrosis (see Figure 7 and page 8 of the specification).

There is no data for the *in vitro* inhibition of alphavbeta6-integrin with EMD 409849, there is no data for the effect of EMD 409849 or any other alphavbeta6-integrin

antagonist against liver fibrosis or any other liver disease either *in vitro* or *in vivo*, and there is no data for the effect of EMD 409849 or any other alphavbeta6-integrin antagonist on cell migration as shown for the alphavbeta3-integrin antagonist EMD 409915 (see above).

Thus, while the specification provides *in vitro* data for the inhibition of cell migration with the alphavbeta3-integrin antagonist EMD 409915, the specification appears to be silent on any correlation between these *in vitro* testing and *in vivo* success in treating liver fibrosis with the alphavbeta6-integrin antagonist EMD 409849. As such, if there is no correlation, then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment chronic liver diseases, is required for practice of the claimed invention.

5. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed in section 3) and in the absence of experimental evidence commensurate in scope with the claims (as discussed in section 4), the skilled artisan would not accept that the alphavbeta6-integrin antagonist EMD 409849 could be predictably be used to treat liver fibrosis.

6. Conclusion

Accordingly, the invention of claim 10 does not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
September 21, 2009.

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612